HAEMONETICS®

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July 19, 1999

Via Federal Express

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 98D-0545
Draft Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods

Dear Sir or Madam:

Haemonetics Corporation submitted comments to FDA on the above-referenced draft guidance on September 15, 1998. As Haemonetics' customers have developed successful apheresis red cell programs, it has become evident that additional comments to the guidance are warranted. These comments are based on customers' actual field experiences with the FDA cleared, Haemonetics apheresis red cell collection technology.

The collection of apheresis red cells is not new. Since marketing approval was granted in the US, more than 150,000 apheresis red cell procedures have been performed by Haemonetics' customers. There is a wealth of worldwide field experience with apheresis red cells and this experience provides valuable information. Analysis of this experience can support the development of sound FDA guidance documents based on actual clinical results.

Enclosed are Haemonetics' additional comments to the draft guidance. Haemonetics welcomes the opportunity to address any questions FDA might have regarding these comments or the collection of apheresis red cells.

Sincerely,

Peter Tomasulo MD /mlz

Peter Tomasulo, MD
Corporate Medical Director and Senior
Vice President, Red Cell Business Unit

Attachment
cc: Judy Ciaraldi (via email: CIARALDI@CBER.FDA.GOV)

98D-0545 SUP 1

Docket No. 98D-0545; Draft Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods

July 19, 1999 Supplemental Comments to September 15, 1998 Comments by Haemonetics Corporation –

Page 2, Section III. A. 2. c. Donor Weight

FDA Guidance Text: "Donors should be weighed prior to each donation. Donors who are not weighed should not undergo the collection of two (2) units of red blood cells by automated apheresis."

Haemonetics requests that the above statement be deleted.

Justification:

Donor Selection Criteria Were Set Conservatively By Haemonetics. The weight requirement to select donors for allogeneic two-unit apheresis red cell ("2RBC") donation cleared by the FDA is based on the objective that no more than 15% of the donor's blood volume should be removed. This requirement is more conservative than the donor weight requirement for manual whole blood donation. In fact, a 110 lb. donor donating 500 ml of blood in a manual procedure loses a larger percentage of his/her total blood volume than the lightest 2RBC donor (see table below).

	Manual Whole Blood Donation Volume = 500 ml		**Two (2) Unit Apheresis Red Cell Donation Volume = 430 ml (two x 215 ml)[1]**	
	Female Donor	*Male Donor*	*Female Donor*	*Male Donor*
Donor Weight	110 lb.	110 lb.	150 lb.	130 lb.
Estimated Blood Volume[2]	3581 ml	4011 ml	4182 ml	4361 ml
Percentage Acute Removal[3]	14%	12.5%	10.3 %	9.9%

Haemonetics chose the 2RBC donor selection criteria so that donor tolerance would be maximized. Clinical trials have established that using these criteria has not resulted in any donor safety issues. No further restrictions are necessary.

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[1] During the automated collection process, the donor's anticoagulated whole blood is pumped into a spinning centrifuge bowl and separated into its components. Plasma and platelets are returned to the donor, the red cells remaining in the bowl are transferred to collection bags. This red cell product consists of 84% red cells and 16% plasma (this is before dilution of the red cells with 100 ml AS-3). This means that when the machine collects 180 ml of red blood cells, the actual product volume collected is (180/0.84) = 215 ml.

[2] Estimated Blood Volumes calculated using the Nådler equation (see AABB Technical Manual , 12th edition, page 731); using a donor height of 5'5" for female donors and 5'1" for male donors, and donor weights as listed in the table.

[3] Percentage Acute Removal = (Donation Volume/Estimated Blood Volume) x 100%.

Safety Was Achieved Without Weighing Donors. The Haemonetics clinical trial that provided safety and efficacy data to the FDA upon which 510(k) clearance was granted for 2RBC allogeneic ("Pre-Market Clinical Trial"), by design did not require the study sites (blood centers) to weigh prospective blood donors. Additionally, Haemonetics agreed to continue the clinical trial beyond pre-market clearance to assist FDA in collecting post-marketing surveillance data on donor tolerance of red cell apheresis ("Post-Market Clinical Trial"). The study design of the Post-Market Clinical Trial also did not require blood centers to weigh donors.

FDA approval to market this technology was granted based on the donor reported symptom rate observed in the Pre-Market Clinical Trial, when donors were not required to be weighed (See Appendix 1).

The Symptom Rate Has Not Changed. The symptom rate observed in the Post-Market Clinical Trial (a partial report is included in Appendix 1; A full report of the Post-Market Clinical Trial will be submitted to FDA by 26 July 1999) is the same or lower than the symptom rate observed in the Pre-Market clinical trial. This study increases the confidence in the original observations. In neither of these trials did Haemonetics make observations which suggest that donors were less honest in providing weight information in advance of a 2RBC donation than when preparing for a manual whole blood donation[4]. In both studies, the reaction rate of the 2RBC donors was nearly equivalent to that of the 1-unit apheresis red cell donors. Based upon review of Haemonetics' records, we can find no allogeneic blood donor clinical trial in which Haemonetics required that a donor be weighed to determine eligibility to participate in a 2-unit donation.

The Requirement To Weigh Donors Is Burdensome And Adds No Value. As most blood donated in the United States is donated on mobile drives, the requirement to weigh apheresis donors would mean that blood centers would have to bring a sufficient number of scales to each blood drive to weigh the potential donors. The scales would have to be validated for mobile use and there would have to be quality control procedures to ensure that the process stayed within desired limits of performance. Ironically, this added burden to blood centers would have the predictable effect of discouraging two unit red cell collection – with its potential for increasing blood availability - at precisely the time that public health officials have begun to warn about likely blood shortages[5]. Last, and of significant importance, not all blood centers currently licensed by FDA for the collection of apheresis red blood cells are required to weigh allogeneic 2-RBC donors.

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[4] The blood safety depends on donor honesty on health and lifestyle questions potentially much more sensitive to a donor than the donor's weight. There is no reason to believe that donors will falsely *over estimate* their weight. Adding this requirement will add time and cost to the procedure without any offsetting benefits to the donor.

[5] Blood center managers including those representing the AABB have indicated in written comments to the FDA that donors should not be weighed.

Summary. The FDA judged that there were sufficient data to grant 510(k) clearance for 2RBC allogeneic blood donations and to grant at least one product license supplement for the same product without requiring measurement of donor weight. Haemonetics is unaware of any data that suggest the need to weigh potential apheresis red cell donors prior to 2-unit donation.

There is currently no regulation requiring that donors giving whole blood via manual techniques be weighed prior to donation. The donation procedure has been deemed by the FDA to be substantially equivalent to whole blood donation and thus 2RBC allogeneic donations should not be held to a higher standard.

Page 3; Section III. C. 3. to Section III. C. 5 (Standard Operating Procedures and Record Keeping)

FDA Guidance Text: "[These parameters should include, but not be limited to, the following:]

3. The hematocrit of the final red blood cell product as determined by the method described in the device operator's manual.

4. An absolute red blood cell volume of each product produced. (Red Blood Cell product hematocrit X Red Blood Cell product volume).

5. A comparison of the calculated donation volume and the pre-determined target volume as determined by the donor's gender and hematocrit."

Haemonetics requests that Section III. C. 3. to 5. be deleted.

Haemonetics is aware that the FDA is considering a requirement that by performing hematocrits and measuring red cell mass on 100 consecutive red cell units, blood centers would be able to confirm that their results match those in the Operator's Manual. Once this is accomplished the blood centers would have to perform hematocrits on 10% of blood units collected.

Haemonetics notes that technical or scientific justification for this additional QC requirement has not been provided and requests that this proposed requirement not be implemented. Haemonetics suggests that instead, apheresis red cells be subject to the same QC requirements as manually prepared red cells.

Justification:

Manual And Apheresis Donations Produce Equivalent Products. In allowing apheresis collection of red blood cells to be marketed, the FDA has deemed apheresis red cells substantially equivalent to manually collected red cells. The CFR makes no specific statements concerning QC procedures for red cell mass or hematocrit in manually collected red cell units. There should be no such requirements for the equivalent apheresis derived red cell units.

Haemonetics Proprietary Technology Ensures Tighter Control Of Hematocrit And Red Cell Volume. Blood centers implementing collection of red blood cells by apheresis must complete process validation, as required by FDA for all blood collection activities. As further described below, the validation procedures performed to date have demonstrated better control of red cell volume and hematocrit than is achieved in manual preparation of red cell units. To require that blood centers continue to determine product hematocrit and absolute red blood cell volume for 10% of apheresis red blood cell products post process validation is inconsistent with demonstrated effectiveness of Haemonetics technology. It is also inconsistent with current practice and requirements for manual red cell preparation.

The red blood cell volume and hematocrit of an apheresis red cell unit are more consistent than those of manually processed red cell products.[6] Haemonetics proprietary technology is designed to collect a precise volume of red cells and to create a specific final hematocrit regardless of donor parameters. This is one of the features of red cell apheresis that was demonstrated in Haemonetics' clinical trials.

Haemonetics has gathered a significant amount of validation and QC data from US blood centers that are routinely performing apheresis red cell procedures. Attached as Appendix 2 is a summary of product quality data for apheresis red cell products.[7] These data, collected by four (4) blood centers, support Haemonetics' position that the proposed QC requirement is unnecessary because variation in volume and hematocrit of apheresis red cell units is far less than variation considered acceptable for manually prepared red cell concentrates. For comparison, Haemonetics has provided data from whole blood derived red cell products that were collected during research trials. Confidence limits have been calculated based on the data submitted by each blood center and are illustrated in Appendix 2. It is apparent that the range

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[6] Absolute red blood cell content of a red cell unit produced from whole blood can range from as low as 153 ml (405 ml whole blood unit, 38% donor Hct) to as high as 247 ml (550 ml whole blood unit, 45% donor Hct). Absolute red blood cell content of a red cell unit produced by apheresis is independent of donor hematocrit.

[7] Some of these data have been submitted to FDA as part of Product License Applications for Red Blood Cells collected by Apheresis. Haemonetics is willing to share the raw data with FDA upon request.

of red cell volumes and hematocrits is well within the parameters set in the operator's manual in every circumstance. The variation is less than the variation seen in manually prepared red cell units. The AABB Standards require simply that the final hematocrit of a whole blood derived red cell unit be less than or equal to 80%[8].

Licensed Blood Centers Do Not Perform These QC procedures on Manually Prepared Red Cell Concentrates. During this data gathering process, it became evident that there is not a significant amount of data available on manually prepared red cell concentrates. Blood center managers informed us that they typically do not QC these products unless there is indication of a problem with the procedure.

Haemonetics Has Provided a Warning System. The red cell protocol software (revision F) includes a message recommending additional QC steps in the rare event that the hematocrit of the packed cells in the centrifuge bowl may not meet specifications.

Summary. Haemonetics proprietary technology collects a specific volume of red cells regardless of the donor hematocrit. We have shown validation data indicating that there is less variation in red cell volume, less variation in hematocrit and that there are internal systems that warn the operator when there is the possibility of being out of specification. The FDA has determined the apheresis red cell product to be substantially equivalent to the manually prepared product and therefore the quality control requirements for apheresis red cell product should be no greater than those requirements for whole blood derived red cell products.

[8] 19th edition AABB Standards, D3.100 Red Blood Cells.

Appendix 1

2-RBC Donor Symptom Proportions – Comparison of 510(k) and Post Marketing Data

Donors experiencing symptoms within three days of donation

Male and Female Donors	510(k) Data Group	Post Marketing Group	
Donor Experience (reported within 3 days of donation)	**Proportion of Donors Reporting Responses (566 donors evaluated)**	**Proportion of Donors Reporting Responses (455 donors evaluated)**	**Statistical significance (p-value)**
None	412 (73 %)	362 (80 %)	--
Mild Experiences:	148 (26%)	89 (19 %)	Yes (p = 0.013)
• **Mild responses**	69 (12 %)	51 (11 %)	No (p = 0.383)
• **Mild citrate effects**	79 (14 %)	38 (8 %)	Yes (p = 0.004)
Moderate Experiences:	6 (1 %)	4 (1 %)	No (p = 0.670)
Severe Experiences:	0 (0 %)	0 (0 %)	--

Definition of donor experience categories:

- Donor experiences were classified as mild, moderate or severe by experts in Transfusion Medicine, based on reported symptoms.
- Mild responses: A combination of any of the following symptoms occurring during the procedure or within the 3 day post donation period; lightheadedness, dizziness, pallor, feeling of warmth, fatigue, headache, chilliness. Donors experiencing these symptoms did not require assistance nor were daily activities affected. None of the collection procedures were interrupted or discontinued.
- Mild citrate effects: Tingling sensations in the donation arm and/or around the mouth. The symptoms were transient, easily tolerated and resolved without intervention.
- Moderate: Any mild donor symptom which was experienced for period of > 30 minutes during the procedure; > 1 day during 3 day follow-up period after the procedure. Donors in this category did not experience a loss of consciousness or require medical aid.
- Severe: Any symptom experienced for a prolonged period of time (> 30 minutes during the procedure; > 1 day during 3 day follow-up period after the procedure), with either loss of consciousness or requirement for medical assistance.

Notes:

The 2-RBC Post Marketing Group reported fewer Mild Experiences and fewer Mild citrate effects.

Appendix 2

Summary of QC and Validation Data from Blood Centers Performing Apheresis Red Cell Procedures

		Volume, Red Cell Concentrate (ml)			RBC Volume (ml)			Hematocrit %		
Center	Sample Size	Sample Mean	Standard Deviation	95% Confidence that 95% of Product Volume Will Be within x of Sample Mean	Sample Mean	Standard Deviation	95% Confidence that 95% of red cell Volume Will Be Within x of Sample Mean	Sample Mean	Standard Deviation	95% Confidence that 95% of Hematocrits Will Be Within x of Sample Mean...
Apheresis Site 1	269	318.13	4.06	± 8.60	179.87	8.22	± 17.4	56.77	2.67	± 5.7
Apheresis Site 2	273	311.8	6.23	± 13.2	178.08	8.68	± 18.4	57.11	4.12	± 8.7
Apheresis Site 3	369	315.78	5.97	± 12.5	177.45	6.75	± 14.2	56.20	2.14	± 4.5
Apheresis Site 4	736	318.06	4.29	± 8.8	179.98	10.72	± 22.0	56.59	3.31	± 6.8
Apheresis Sites COMBINED	1647	319.37	6.73	± 13.2	179.25	9.28	± 18.1	56.65	2.90	± 5.7
Manual Preparation*	21	311	19	± 52.2	186	16	± 44.0	60.0	3.6	± 9.9

*Holme et al. Vox Sang 1998; 75:212.

Notes:

The "95% Confidence" columns provide the following information:

There is a 95% likelihood that in future measurements, 95% of the units measured will have values (for Volume, Red Cell Concentrate; for RBC Volume and for Hematocrit) within the given tolerance limits of the calculated sample mean.

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